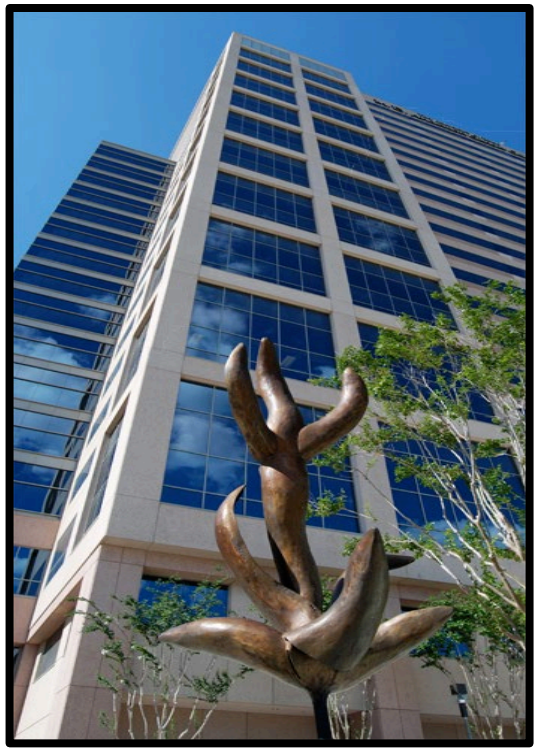


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

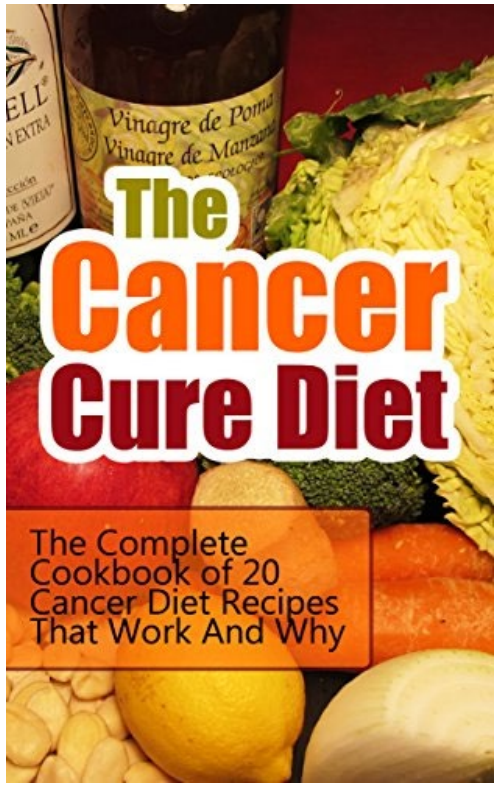
Gut Check: Exploring the Diet-Microbiome Axis and its Impact on Immunotherapy Outcomes

Carrie Daniel-MacDougall, PhD, MPH

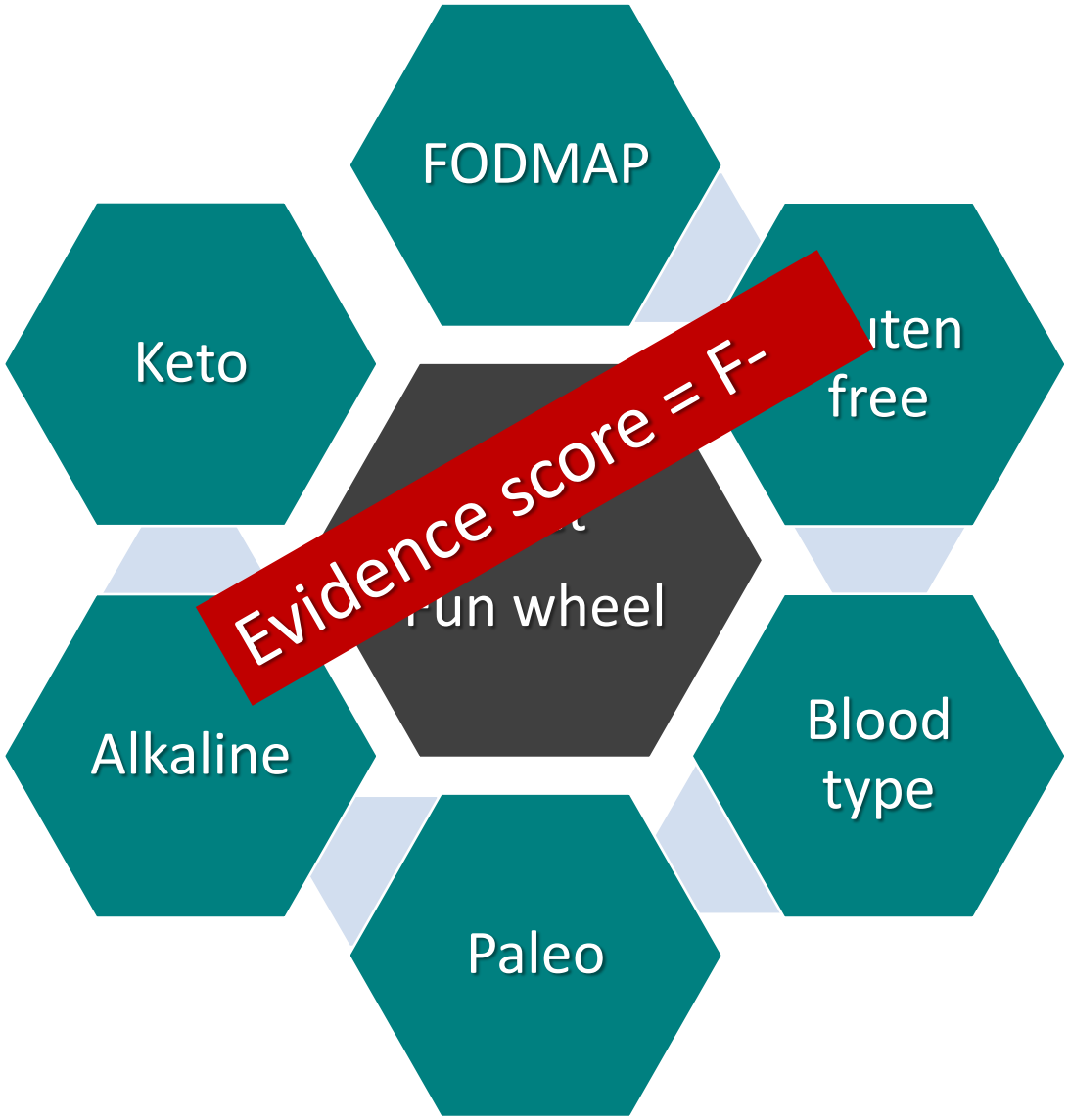
Associate Professor, Department of Epidemiology
Director, Bionutrition Research Core
Resource Leader, Center for Energy Balance in Cancer Prevention and Survivorship
Nutrition and Epidemiology lead, Platform for Innovative Microbiome and Translational Research

No COI/disclosures

Patient: "What should I eat?"



Cancer patients independently exploring different dietary strategies

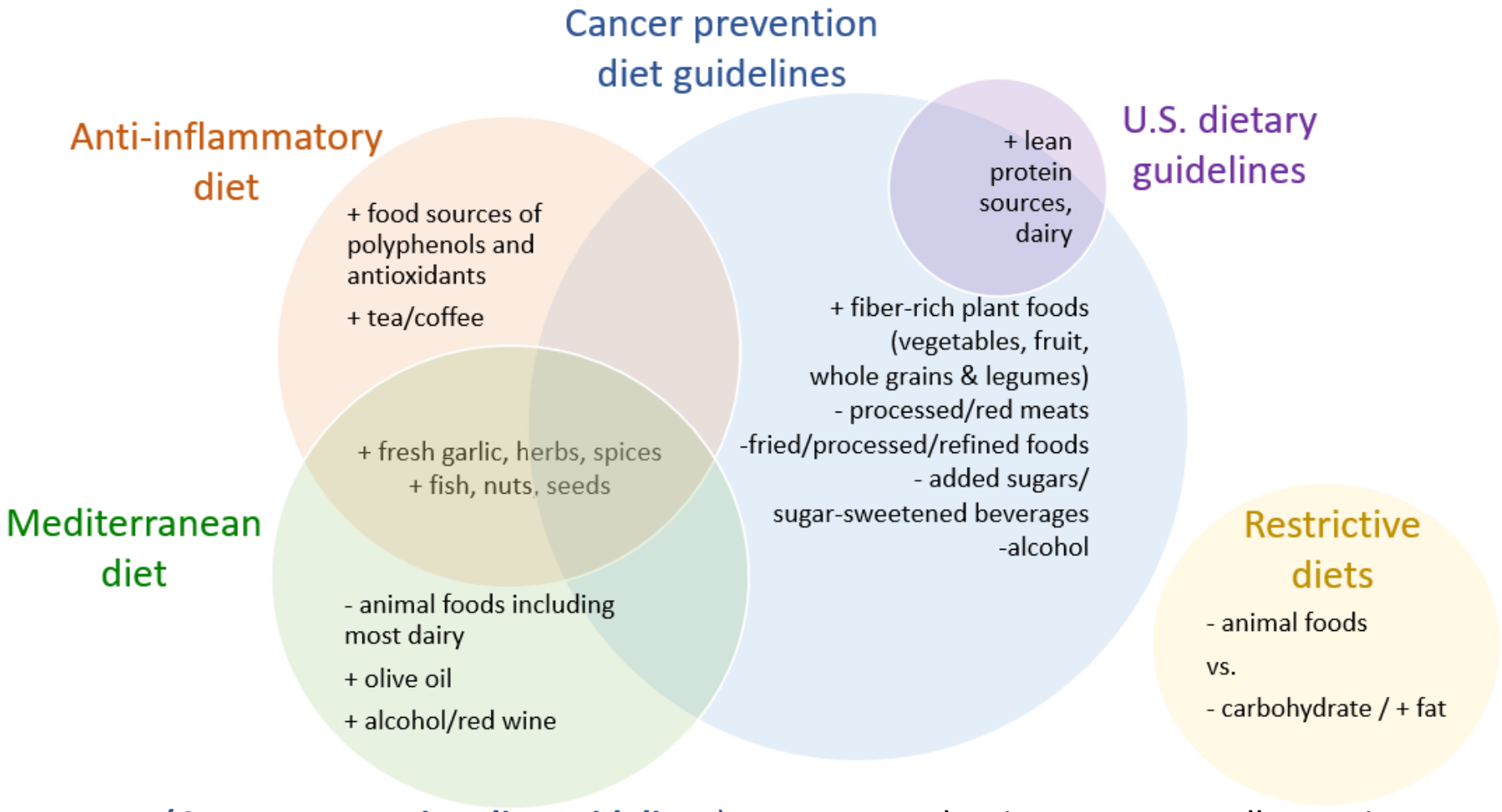


- No secret formula or evidence-based dietary guidelines for cancer patients.
- Lack of dietary data collection in trials and clinical cohorts
- Lack of prospective / interventional dietary studies demonstrating change in response
- The best we can do is extrapolate from evidence-based cancer *prevention* guidelines (AICR, ACS)

*Personal communication MD Anderson Clinical Nutrition

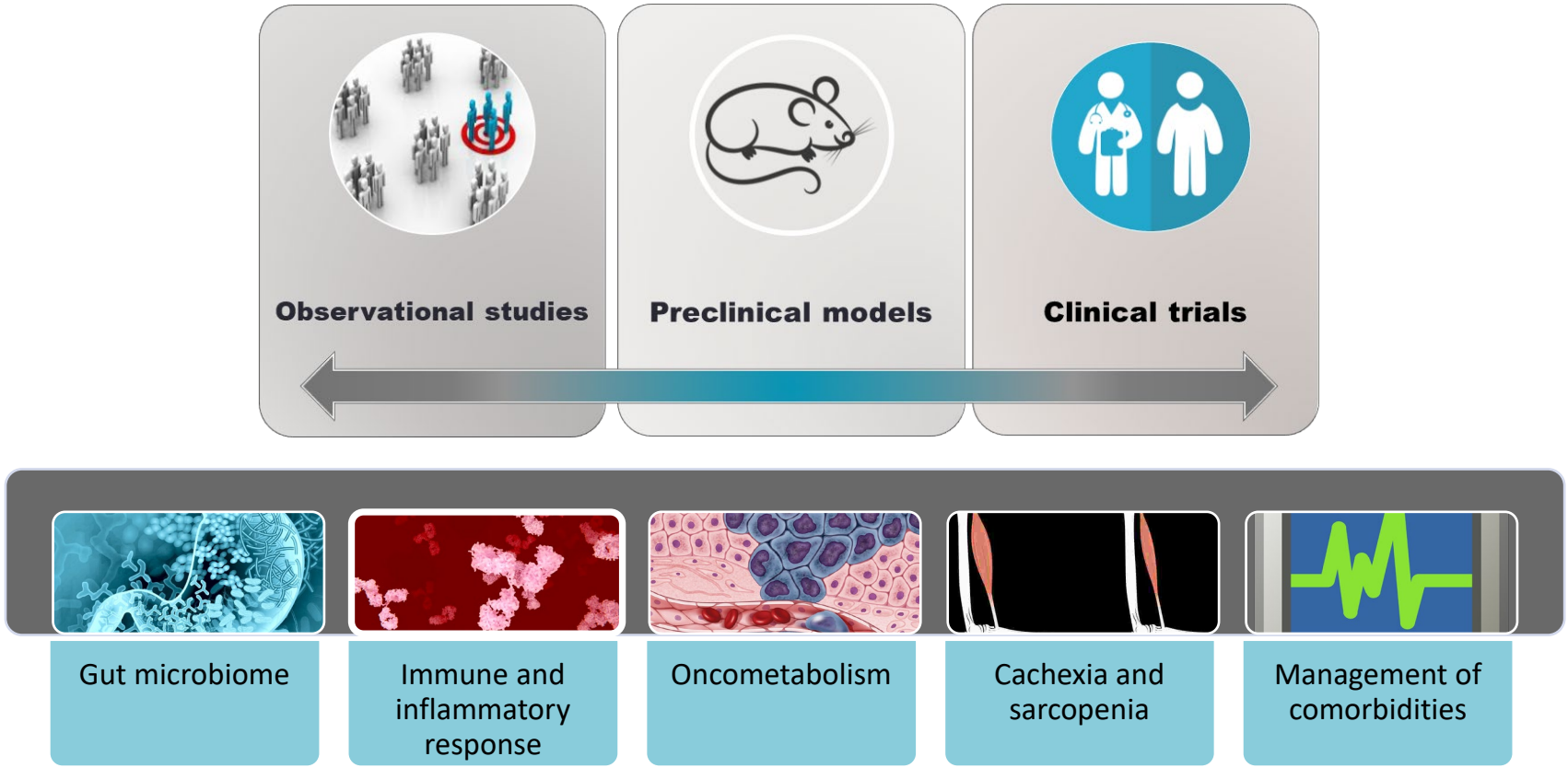

LIMIT CONSUMPTION OF RED AND PROCESSED MEAT
LIMIT CONSUMPTION OF SUGAR SWEETENED DRINKS
LIMIT CONSUMPTION OF 'FAST FOODS' AND OTHER PROCESSED FOODS HIGH IN FAT, STARCHES OR SUGARS
LIMIT ALCOHOL CONSUMPTION
World Cancer Research Fund
American Institute for Cancer Research
EAT A DIET RICH IN WHOLEGRAINS, VEGETABLES, FRUIT AND BEANS
DO NOT USE SUPPLEMENTS FOR CANCER PREVENTION
OUR CANCER PREVENTION RECOMMENDATIONS
Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk. Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.
BE PHYSICALLY ACTIVE
FOR MOTHERS: BREASTFEED YOUR BABY, IF YOU CAN
BE A HEALTHY WEIGHT
AFTER A CANCER DIAGNOSIS: FOLLOW OUR RECOMMENDATIONS, IF YOU CAN
www.aicr.org

Dietary patterns linked to cancer survival in prospective studies



Central index or pattern (Cancer prevention diet guidelines) represents what is common to all. Exterior connected circles show unique emphasis (+) or exclusions (-) of each diet. **Restrictive diets** (e.g., vegan vs. ketogenic) restrict or exclude certain types of foods or sources of nutrients but are otherwise flexible regarding food choices to meet those goals.

Prepared by CR Daniel for invited review in progress



Research framework for moving from observational studies with extended outcomes to specific preclinical and clinical studies assessing the biologic effects and underlying mechanisms linking diet to cancer survival.

Prepared by CR Daniel for invited review in progress

“Modifiable factors” in cancer patients

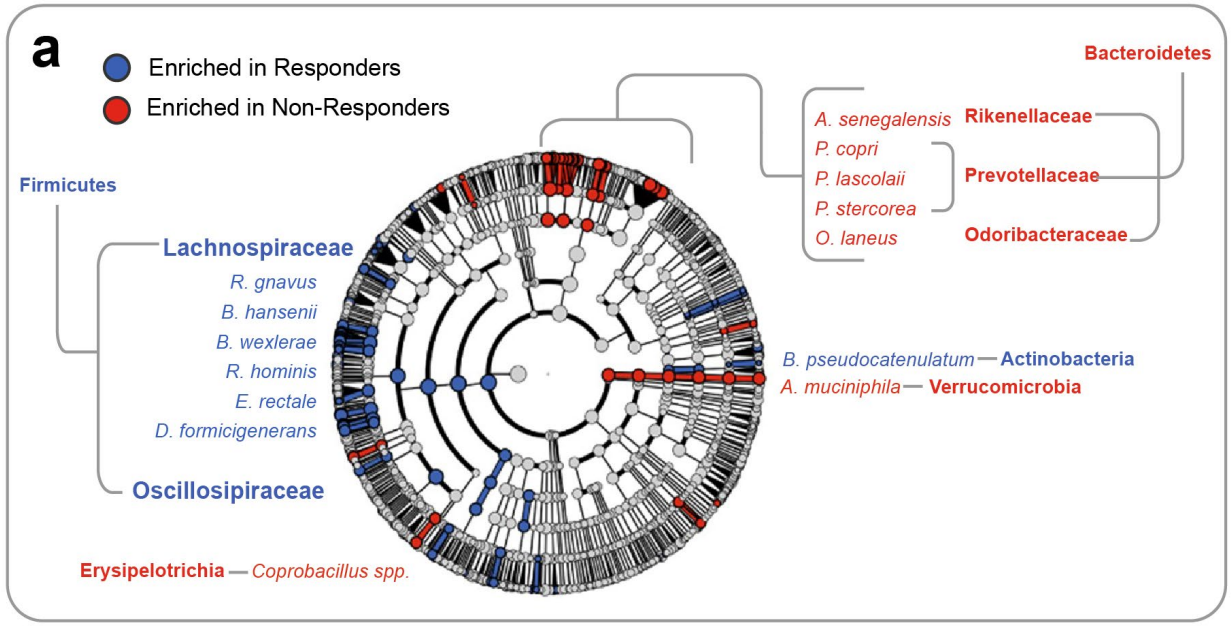
- Goal is effective and durable treatment response to extend survival
- Treatments constantly evolving and changing
- Obesity and poor diet are well established in cancer risk and increasingly recognized in cancer progression and outcomes
- The link between the gut microbiome and therapeutic response (or resistance) is shaping new research priorities for patients with cancer
- Patient attributes/habits may synergize with or inhibit treatment tolerance and efficacy

McQuade, Daniel, Helmink, Wargo
Lancet Onc 2019

Daniel & McQuade
Trends in Cancer 2019

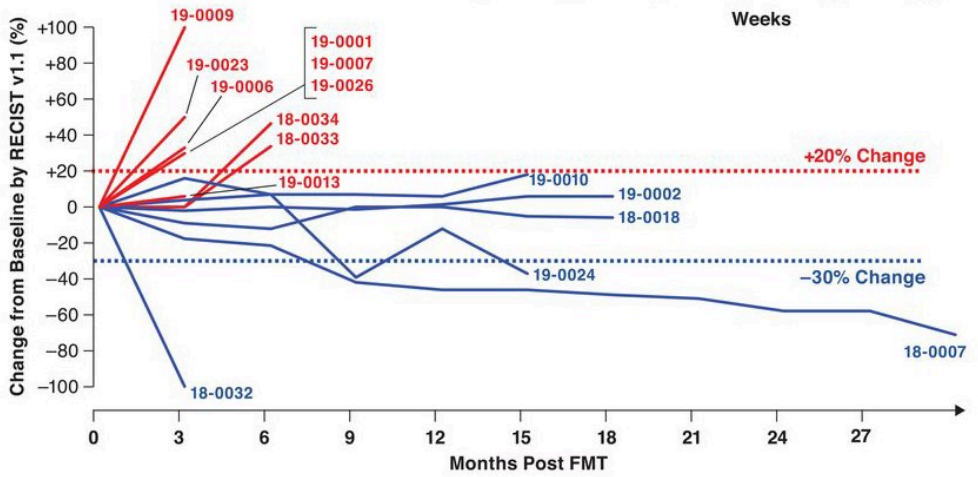
Gut microbiome as biomarker and target to enhance ICB response

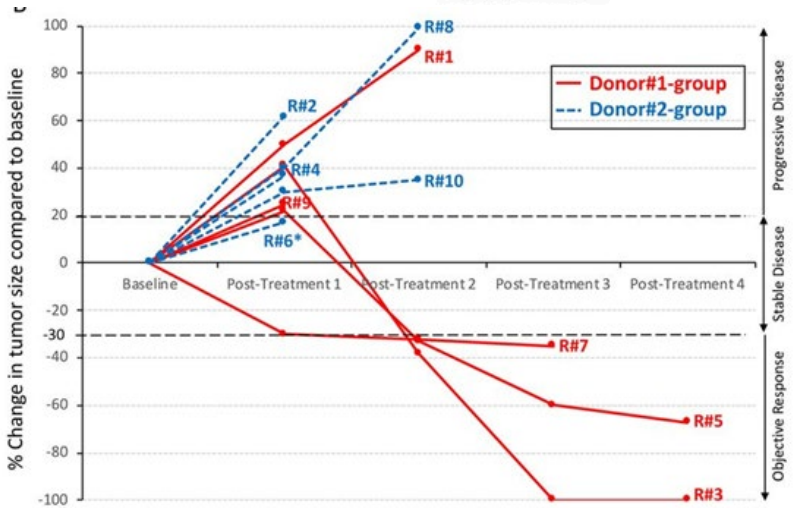
The gut microbiome is associated with response to ICB



McCullough *Nature Medicine* 2022

2L PD1 + FMT induced response in 20-30% of PD1-resistant melanoma





Davar *Science* 2021

Baruch *Science* 2021

A range of factors are known to modulate the microbiome

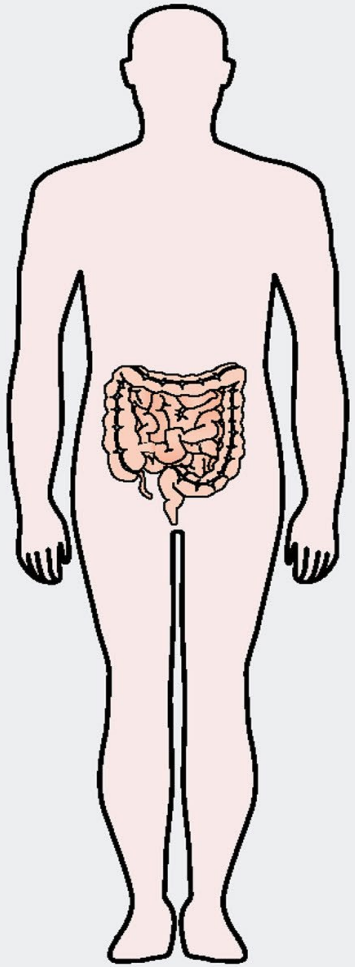
External factors (modifiable)

Host factors (non-modifiable)

Medications
(antibiotics, probiotics, proton-pump inhibitors, metformin, anti-depressants)

Diet
(fibre-rich, plant-based diet *vs* typical western diet)

Demographics
(age, sex)



Host genomics
(genetic polymorphisms [HLA, genes affecting innate immune function])

Anthropometrics
(BMI)

Environment
(Geography, cultural preferences, environmental exposures)

Psychological factors
(depression, stress, etc)

Figure in "Modulating the microbiome to improve therapeutic response in cancer," *Lancet Onc* 2019

It begins with food and ends with… 💩

Prebiotics

Non-digestible fiber compounds that stimulate the growth and activity of beneficial gut microorganisms.

Probiotics

Live microorganisms that inhabit the microbiome and confer health benefits when consumed in sufficient amounts.

Synbiotics

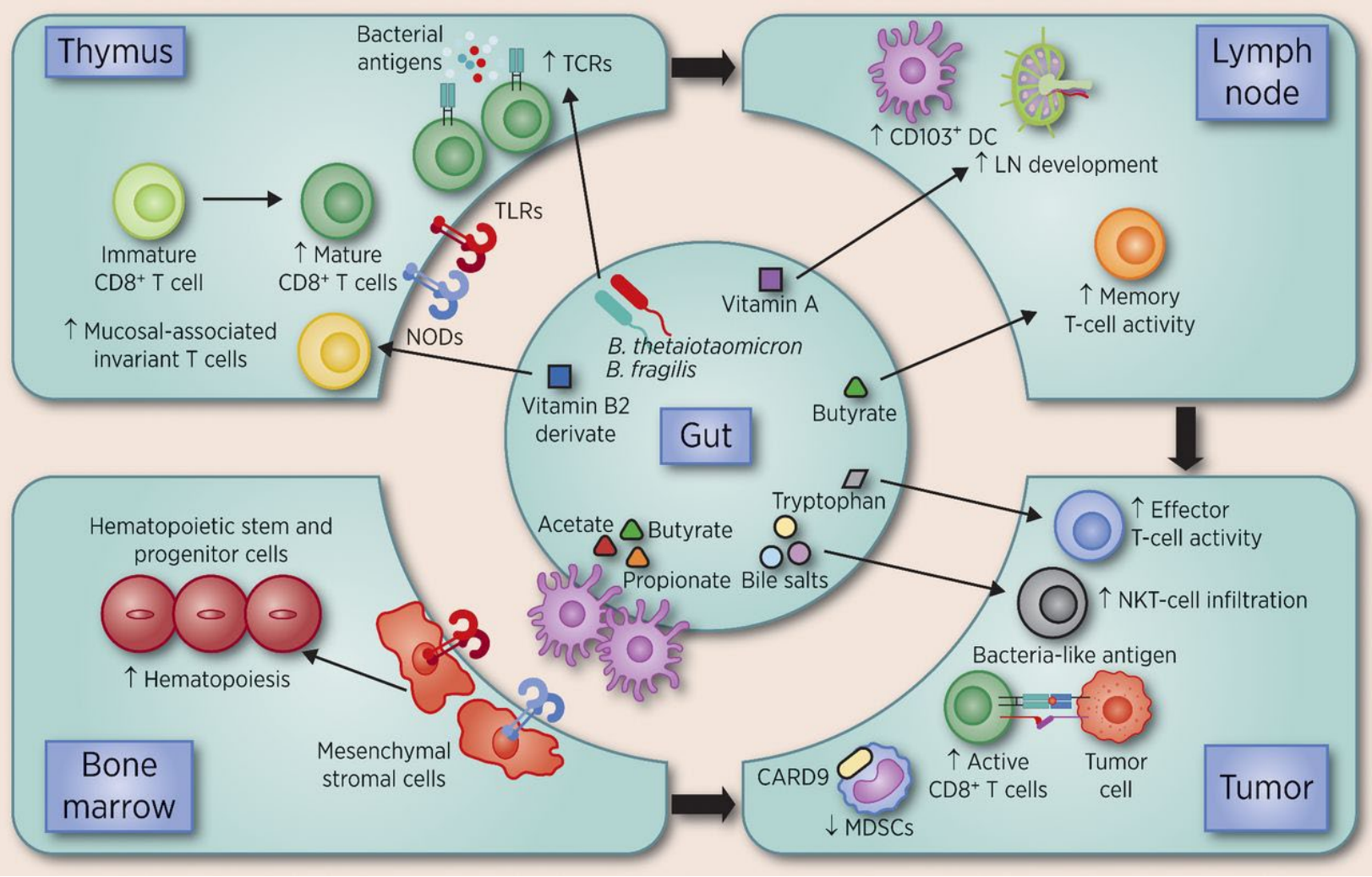
A combination of prebiotics and probiotics.

Postbiotics

Products of prebiotic and probiotic activity that mimic some of the same benefits as probiotics, but also offer additional health benefits.

Figure from: https://www.optimoz.com.au/collections/gut-health (not an endorsement of website or products)

Mechanisms of immune modulation by the gut microbiota



The gut microbiota may affect immune cells playing key roles in antitumoral immunity via:

- activation of pathogen recognition receptors
- molecular mimicry initiating immune responses against cancer antigens that are similar to bacterial ones
- **metabolic modulation using vitamins, short-chain fatty acids, bile salt, or amino acids that promote favorable intracellular processes among host cells**

Figure in “Gut Microbiota and Antitumor Immunity: Potential Mechanisms for Clinical Effect”, *Cancer Immunol Res* 2021

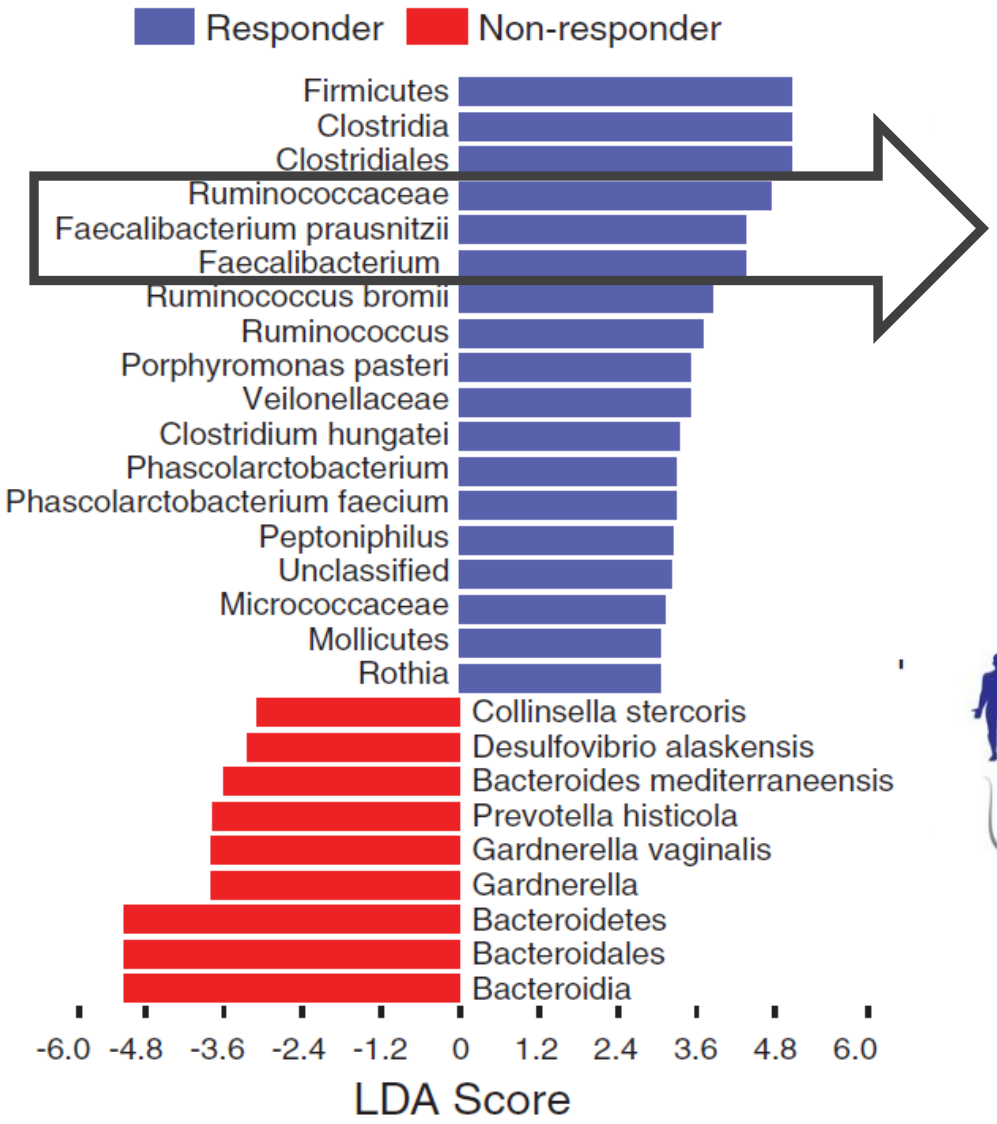
Team Science

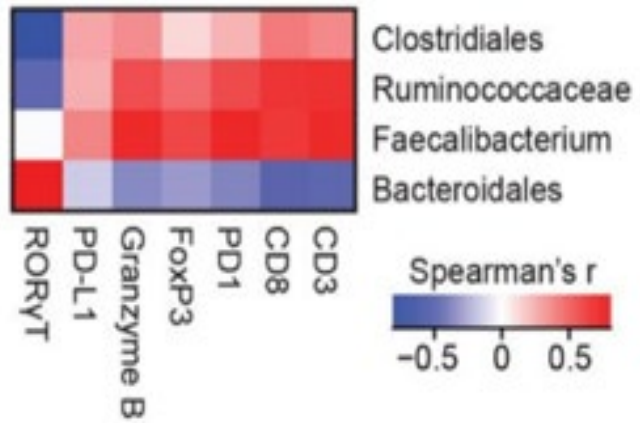
- Collaborative efforts across research and clinical teams → develop strategies to target the microbiome in cancer patients with the overall goal to improve treatment response rates, reduce toxicity and extend survival.

- Over the past 5+ years, we built patient cohorts and clinical trials in melanoma (and expanded this experience to other cancers) integrating measures of various host factors not captured in the EMR
  - Diet, physical activity and other aspects of lifestyle
  - Antibiotic use
  - Supplement use
  - Patient-reported outcomes

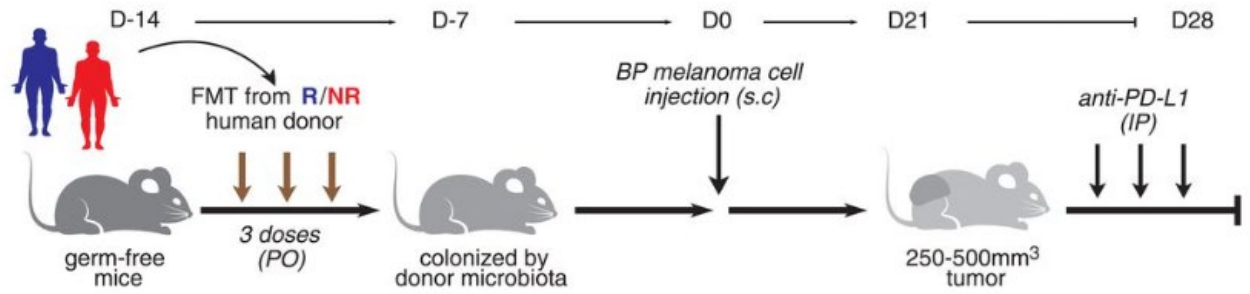
- Parallel mechanistic studies

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients



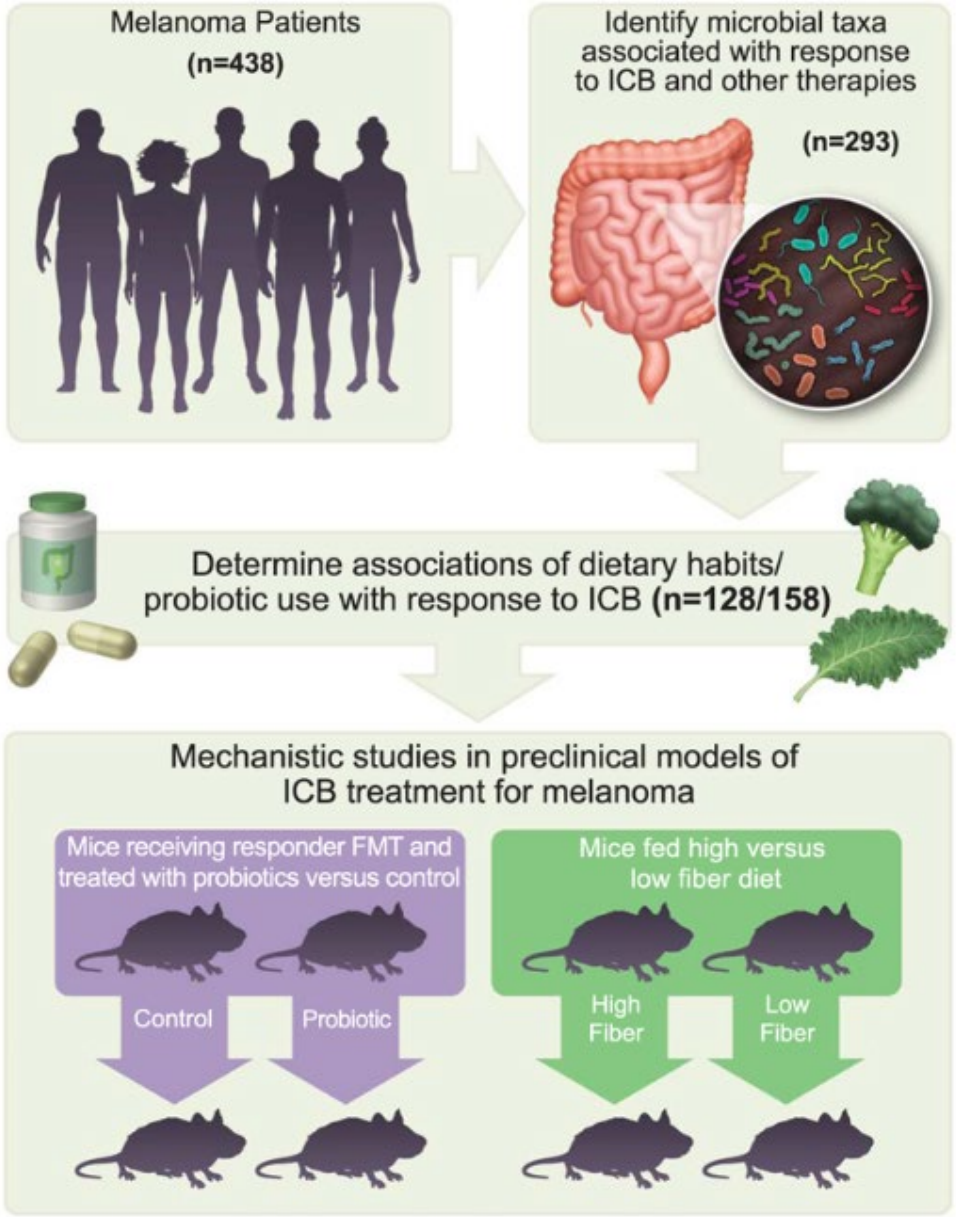


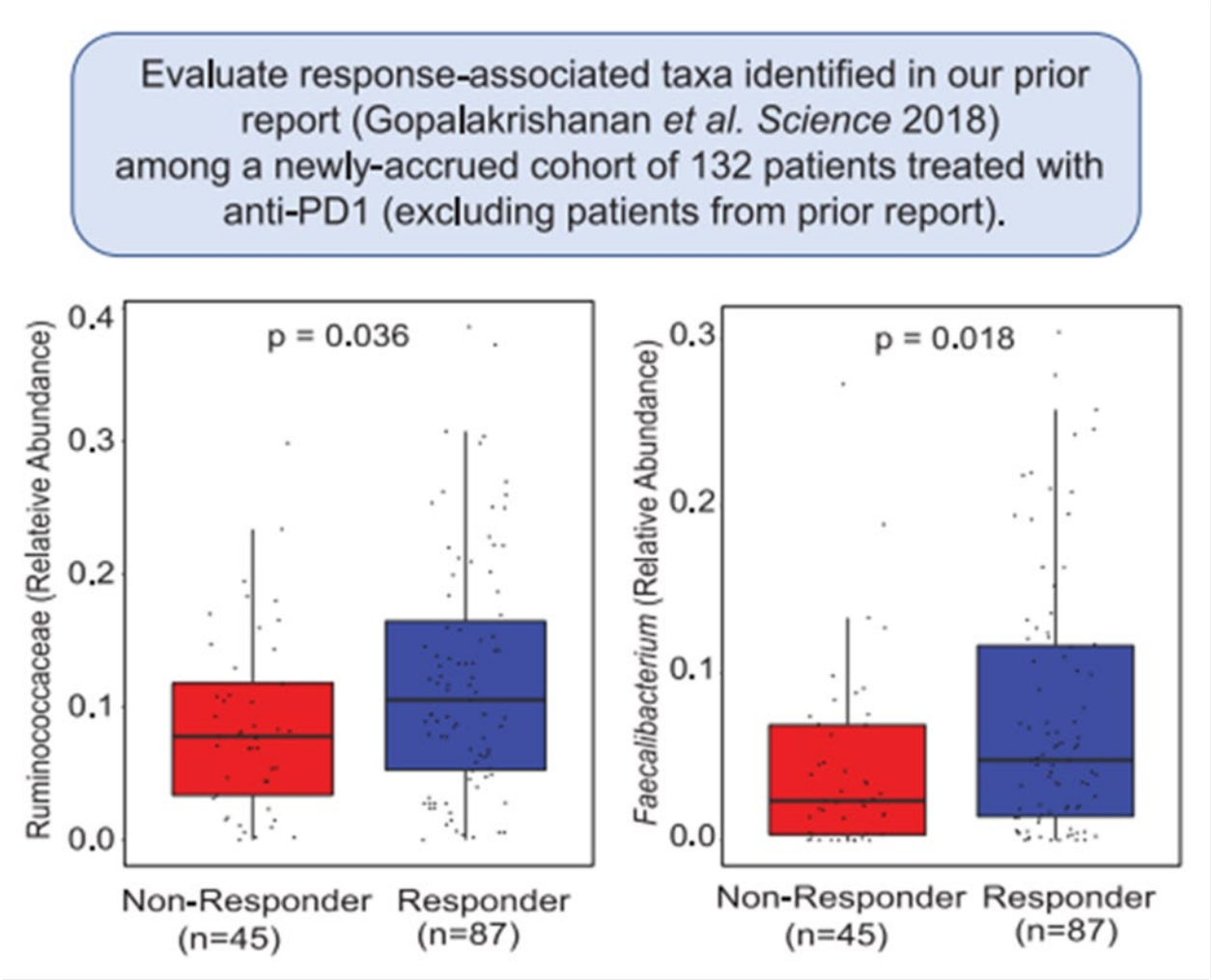
Jennifer Wargo



Gopalakrishnan *et al. Science* 2018

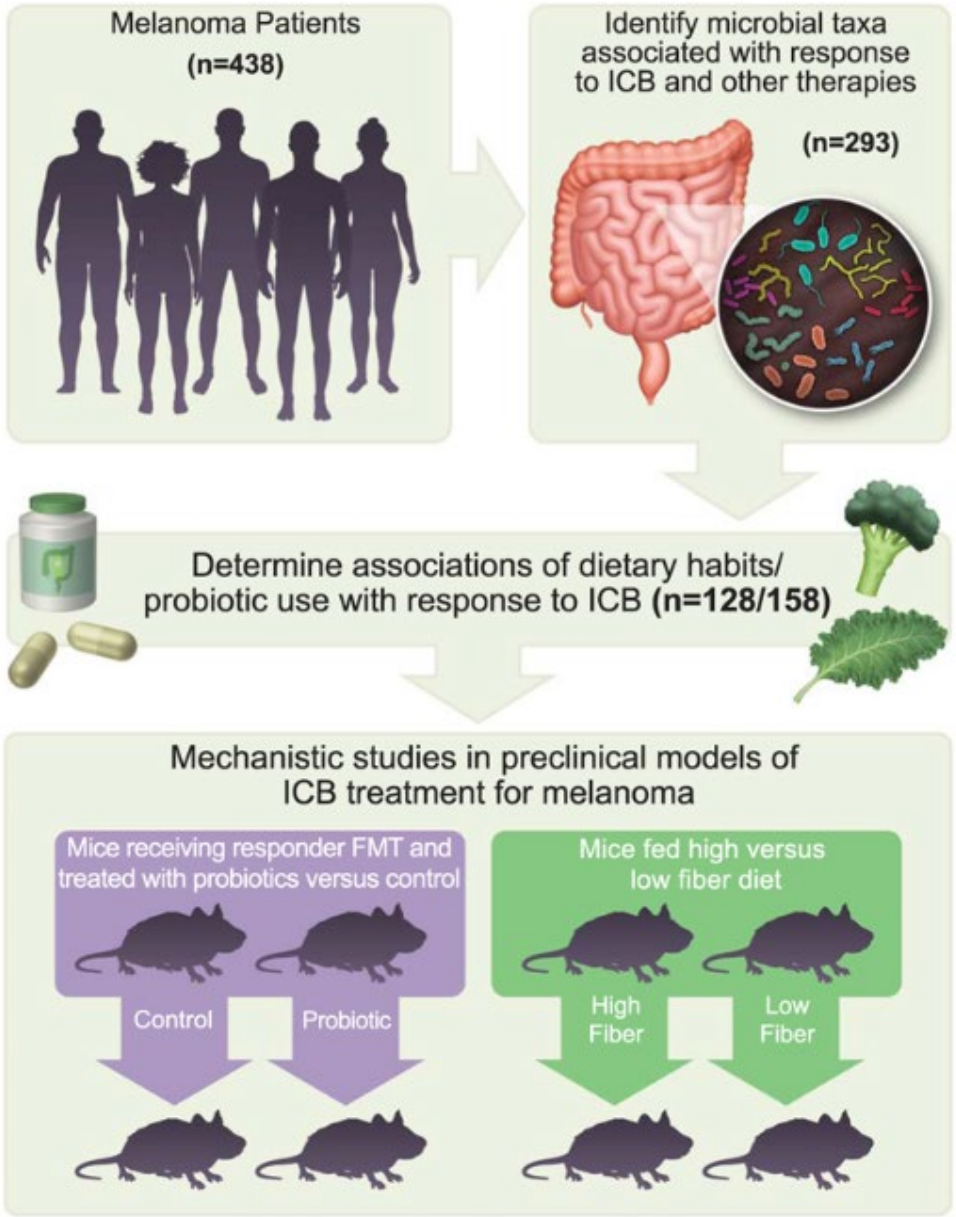
Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

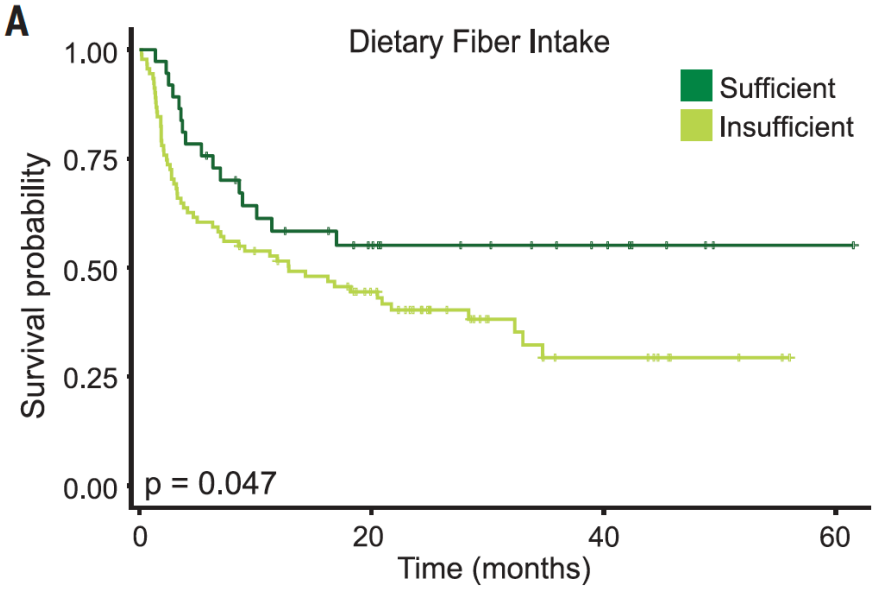




Spencer *et al. Science* 2021

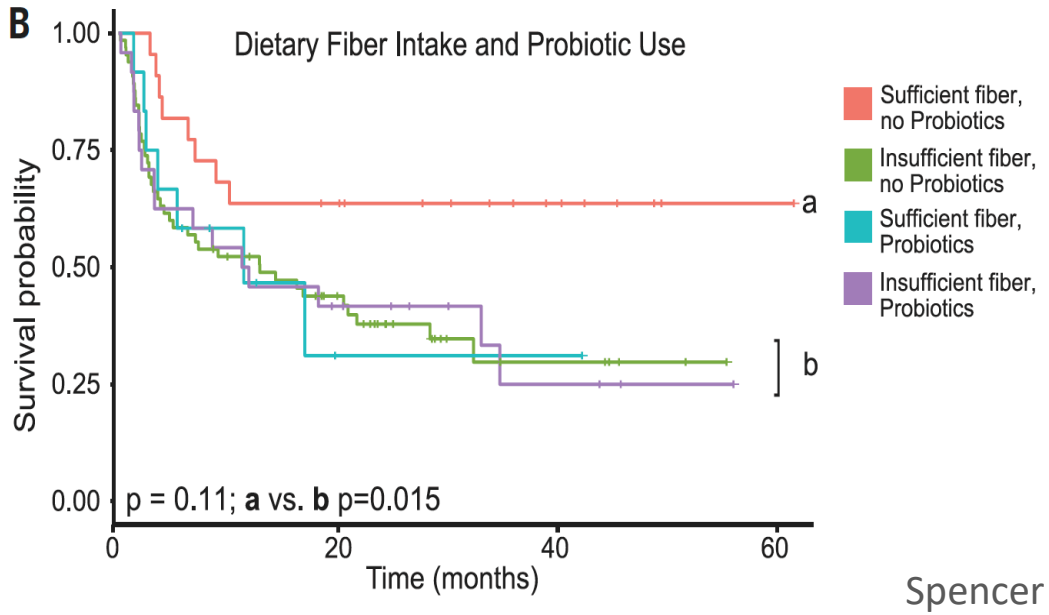
Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response





Multivariable-adjusted (subtype, stage, LDH, BMI) HR and 95% CI per 5 g/day increase:

0.71 (0.52, 0.98)



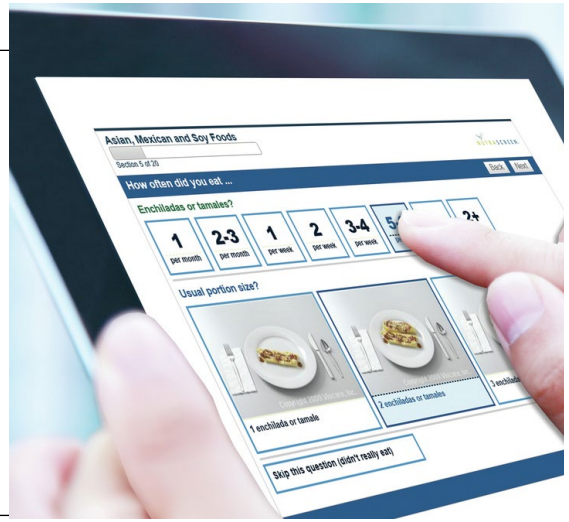
Fiber + no probiotics vs. else 0.44 (0.21, 0.92)

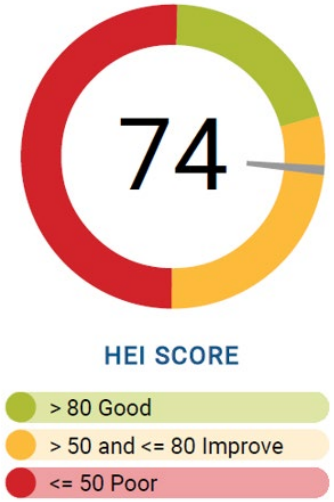
Spencer *et al. Science* 2021

Dietary habits in stage IV melanoma survivor cohort: a population at-risk

Patients responded to queries asking about food consumption over the past month

Nutrient or Food group	Min	Mean	Max	*Recommendation*
Fiber	12	**18**	36	*Below (25-30 g daily)*
Calcium	768	**1035**	1399	*Below (1000-1200 mg daily)*
Whole grains	0.3	**0.8**	1.7	*Below (3-5 servings daily)*
Added Sugar	10	**17**	37	*Above (limit 9 tsp daily)*
Dairy	1.0	**1.6**	2.8	*Below (3 servings daily)*
Total fruit, veg + legumes	1.6	**2.9**	6.6	*Below (5 servings daily)*
Vegetables + legumes	1.1	**1.9**	4.1	*Below (3 servings daily)*
Fruit	0.4	**1.0**	4.0	*Below (2 servings daily)*





- >70% fell within criteria of “insufficient dietary fiber intake” associated with NR and shortened PFS (*Science* 2021)
- Overall, distributions were similar to those observed among patients in active treatment with fruit, vegetables, legumes, and whole grains contributing similarly to dietary fiber intake.
- 67% reported following a special diet
- Further investigation into the role of long-term side effects and microbiome profiles

Jennifer McQuade

Unpublished/in submission data: PLEASE DO NOT SHARE OR POST; Vioscreen figures from: https://www.viocare.com/

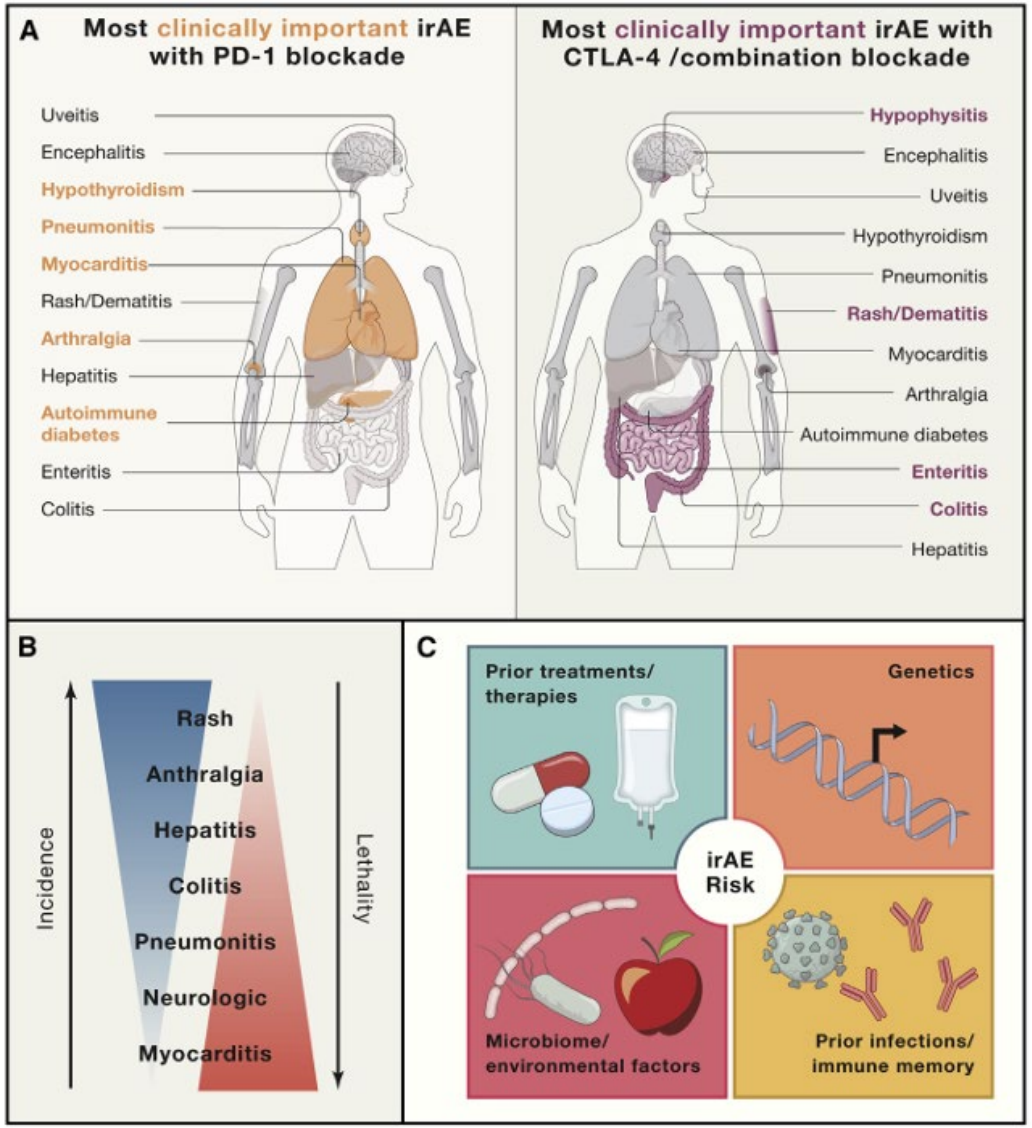
Considerations and challenges ahead to modulate a patient's microbiome

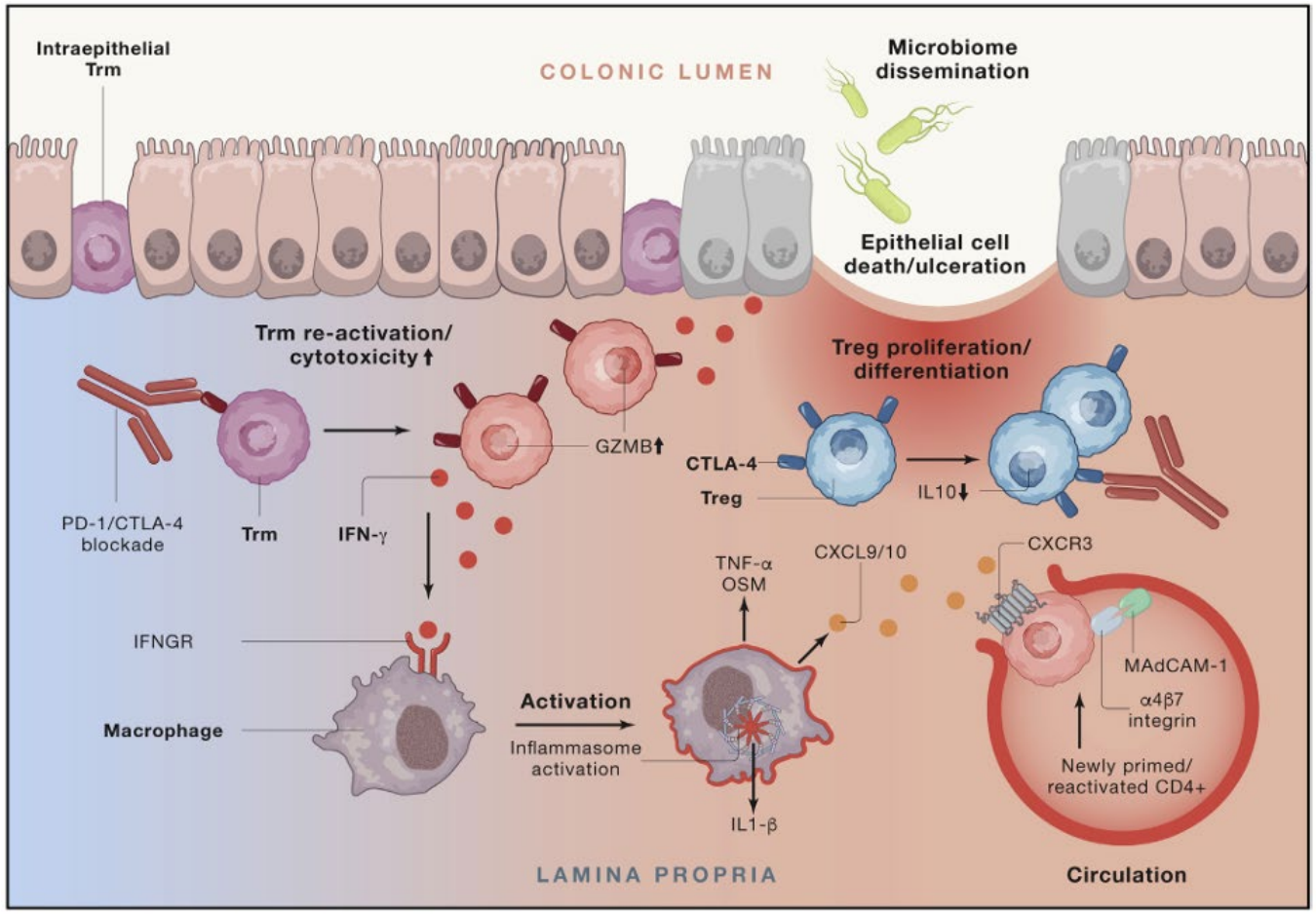
	Advantages	Disadvantages	Considerations
Faecal microbiota transplant	Transplantation of entire ecosystem; direct	Scalability (difficult to access and expensive); procedural risks; potential to transfer other diseases	Donor selection (complete responder to faecal microbiota transplant *vs* healthy donor); delivery mechanism; need for conditioning regimen; how to sustain; banking for potential future autologous transplant
Probiotics and bacterial consortia	Easy to use; affordable; accessible	Variable engraftment in setting of competing commensals; potential for lowering overall microbiome diversity; varying bioavailability; insufficient regulations on quality control	Use of spores *vs* live bacteria; which bacteria to include; personalisation; need for conditioning regimen
Prebiotics (eg, fibre supplements)	Easy to use; affordable; accessible	Whole food might be more important than isolated nutrient supplements (regulated as food rather than drugs)	Single fibre *vs* mixture; predictability of response given resident bacterial community
Diet	Holistic change that might have other health benefits	Low compliance; difficult to sustain; varied effects	Whether to target specific nutrients *vs* overall pattern; dose needed for target modulation; duration needed; predictability of modulation given host variation in microbiome and metabolism

McQuade, Daniel, Helmink, Wargo
Lancet Onc 2019

Daniel & McQuade
Trends in Cancer 2019

Clinical benefit of immunotherapy (response) balanced by inflammatory toxicities (irAE): microbiome central in both

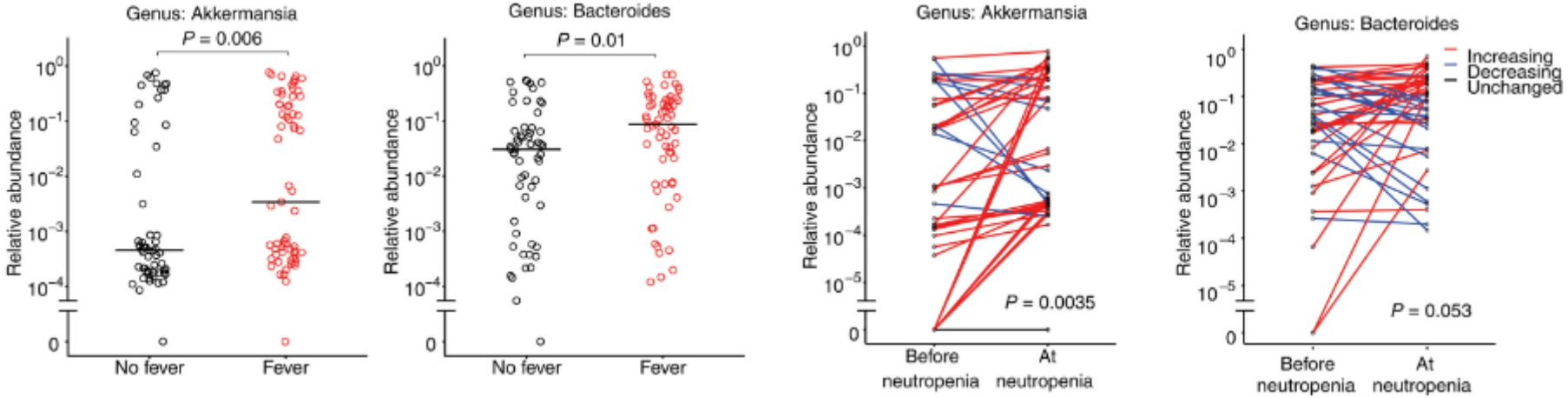




Figures in “Understanding and treating the inflammatory adverse events of cancer immunotherapy,” *Cell* 2021

Diet, metabolites, and intestinal mucus link the gut microbiome to fever after cytotoxic cancer treatment

Mucin-degrading intestinal bacteria associated with development of fever after onset of post-HCT neutropenia.



Robert Jenq

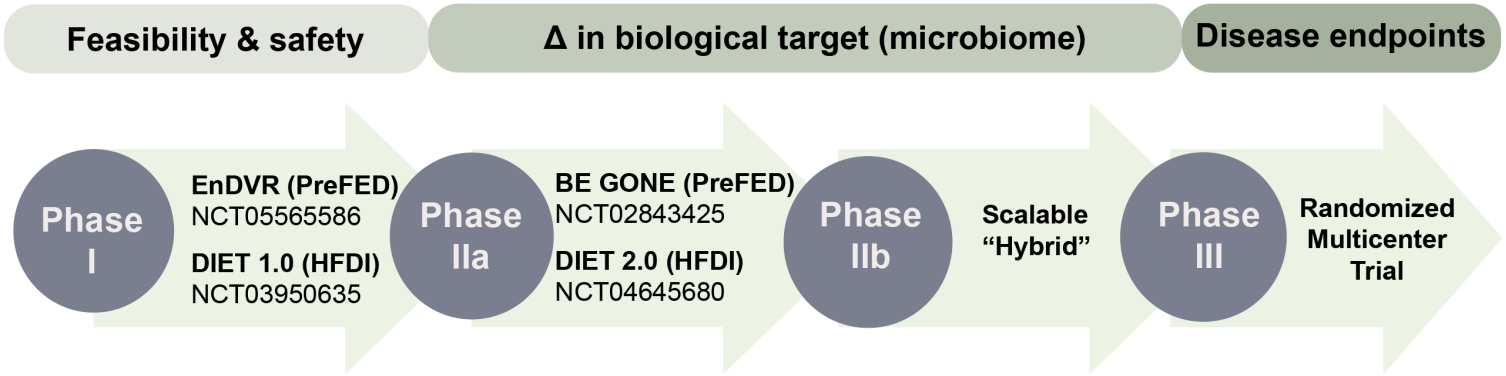
Preclinical:

- Radiation or chemotherapy changes the composition of intestinal bacteria, leading to increases in *Akkermansia* and thinning of the (protective) colonic mucus layer
- Restriction of energy (calories) is sufficient to produce changes in the composition of the intestinal bacteria similar to those seen after cytotoxic therapy

Clinical: Further investigation of patients' diets and microbiota-supporting nutrients

Schwabkey *et al. Science Transl Med* 2022

A phased approach to dietary intervention studies



End-Goal:
Diet interventions and/or rationally designed pre/pro/syn-biotics to improve disease outcomes

DIET 1.0: Fully controlled high-fiber feeding study in n=10 melanoma survivors

- Demonstrated feasibility
- High compliance with consuming diet and providing fecal and blood specimens
- Tolerable
- Shift in microbiome and circulating metabolites

DIET 2.0: Controlled high-fiber feeding study melanoma patients starting SOC immunotherapy

- Enrollment completed
- Correlative studies are on going

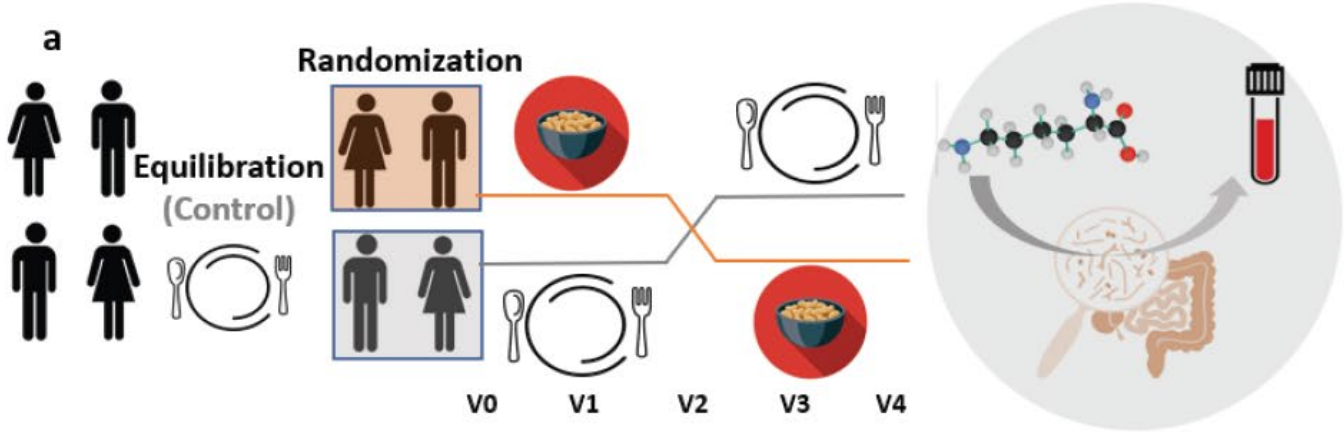
EnDVR (PreFED) trial in MD Anderson employees

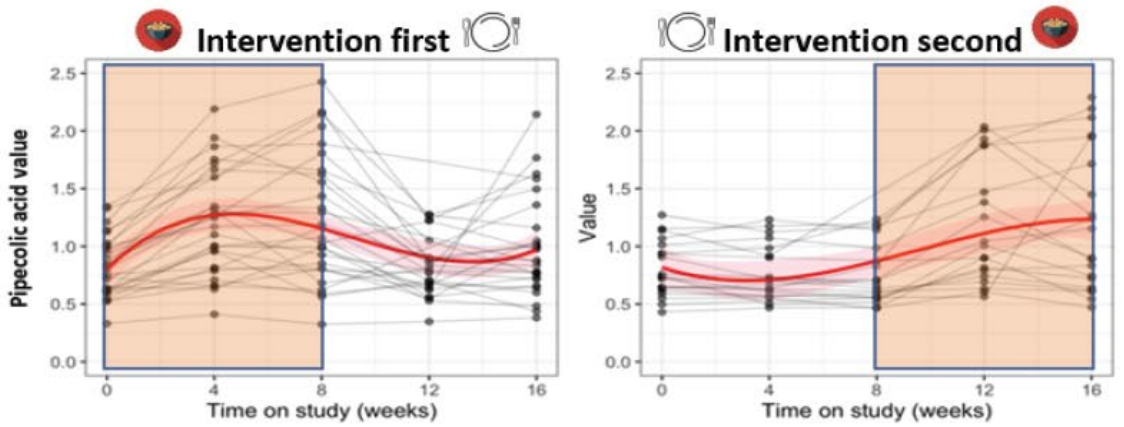
- Randomized to PreFED (snacks and meal counseling) vs HFDI
- >90% snack compliance and exceeded the target of +4 prebiotic food servings
- PreFED is an equally effective regimen as HFDI to stimulate key features associated with ICI response

BE GONE trial in overweight and obese colon cancer survivors

- Targeted food provision + RD counseling approach
- Tolerable
- Increases diversity (inverse Simpson index) and candidate taxa
- Anti-inflammatory metabolites and proteomic markers

Modulating a prebiotic food source (beans) influences inflammation and immune-regulating gut microbes and metabolites: insights from the BE GONE trial





Colorectal cancer survivors:

- Surveillance colonoscopy and GI Med Onc follow-up patients with issues jointly managing gut and metabolic health (obese)
- Half on statins and/or metformin
- Adequate bowel length and "normalized" bowel habits

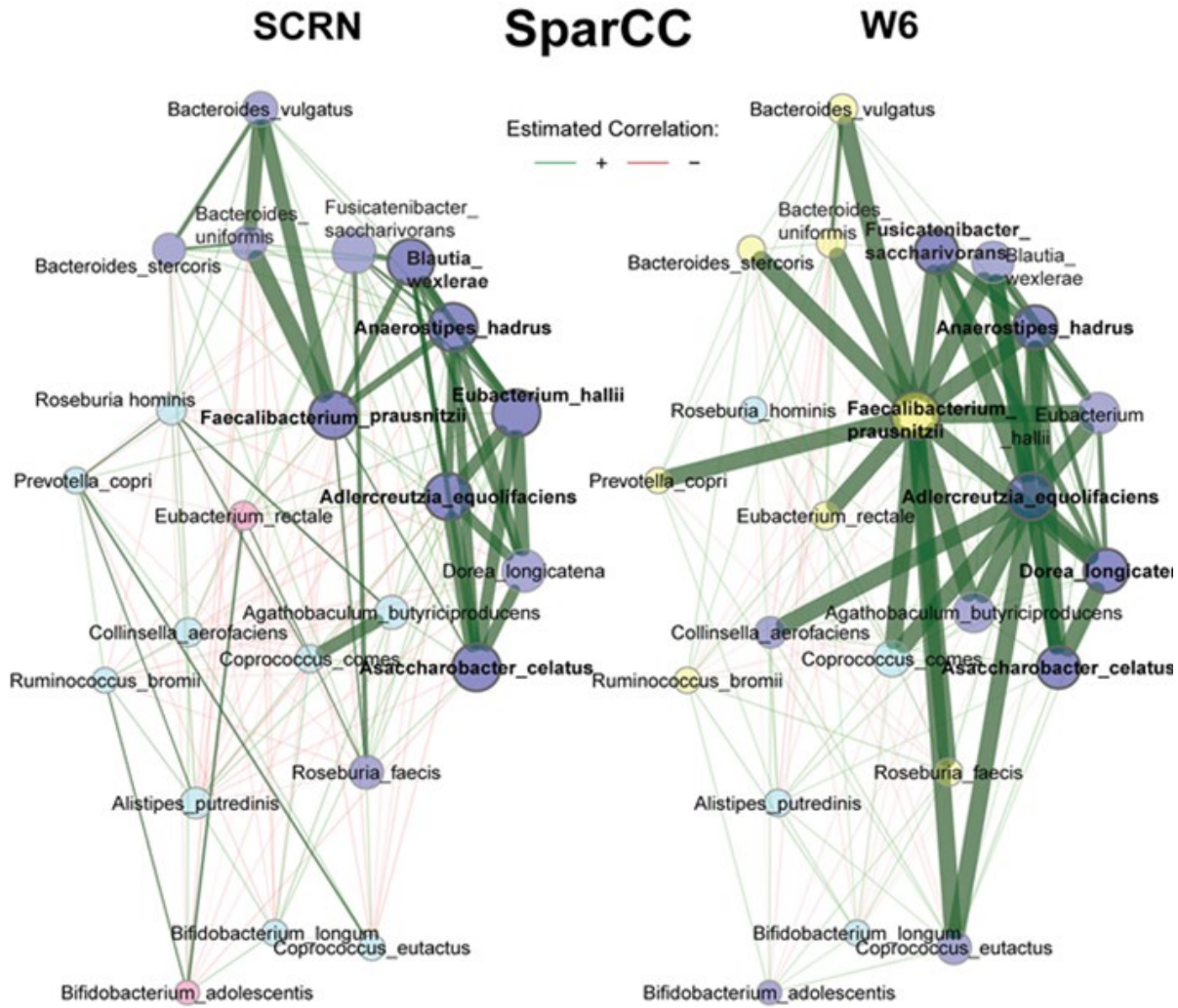
Findings:

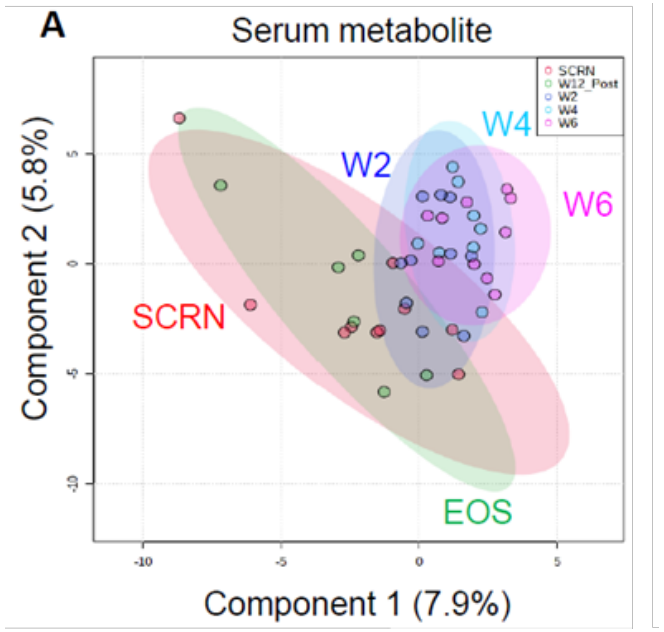
- 87% completed the 16-week trial; carefully monitored side effects
- ↑ diversity and shifts in multiple bacteria indicative of prebiotic efficacy, including ↑ *Faecalibacterium, Eubacterium* and *Bifidobacterium*
- Circulating metabolome showed parallel shifts in nutrient and microbiome-derived metabolites that regressed upon returning to the usual diet
- Shifts in proteomic biomarkers of intestinal and systemic inflammatory response

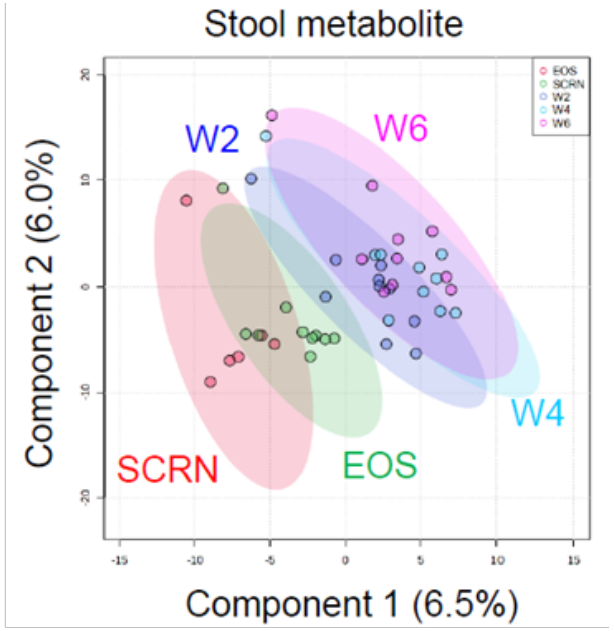
eBioMedicine
Part of THE LANCET *Discovery Science*

NCT02843425

DIET 1.0: high fiber feeding study in melanoma survivors

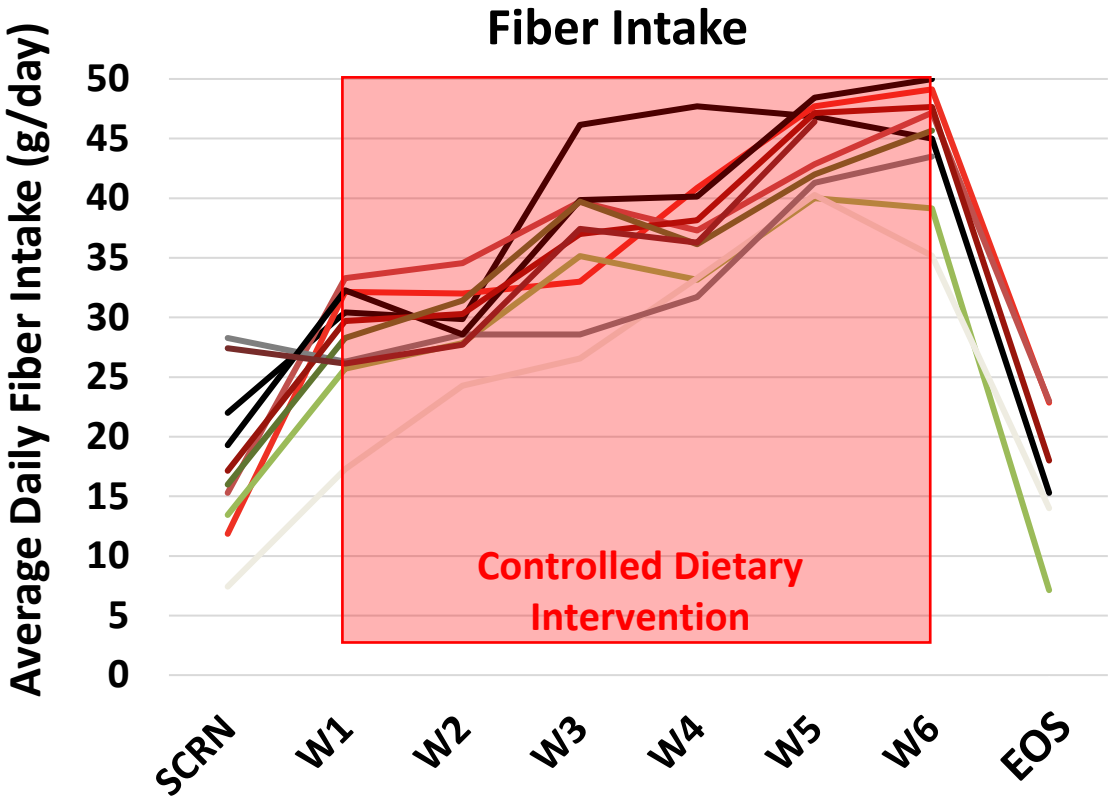


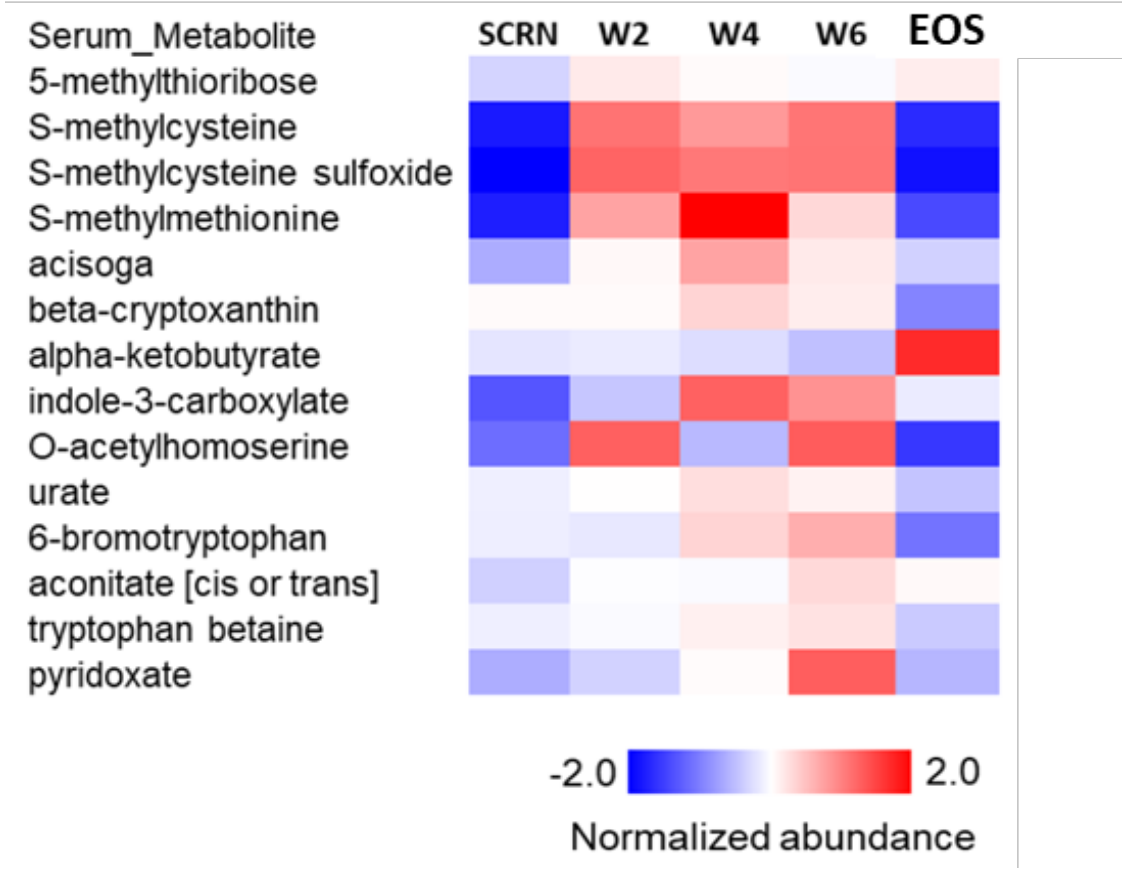




Unpublished/in submission data: PLEASE DO NOT SHARE OR POST

DIET 1.0: post-study reversion to usual diet and reversion of metabolites





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DIET 2.0

Metastatic melanoma patients receiving SOC ICIs

RCC patients receiving SOC ICIs

Cohort 1: Adjuvant (n=21)
- Resected Stage II/IV melanoma with planned initiation of adjuvant ICI

Cohort 2: Unresectable (n=12)
- Unresectable stage III or Stage IV melanoma with planned initiation of ICI

Cohort 3: Neoadjuvant (n=12)
- Resectable melanoma with planned initiation of neoadjuvant ICI

Cohort 4: Unresectable RCC (n=12)
- Metastatic clear-cell RCC with planned initiation of ICI

Dietary Intervention

Each cohort randomized 2:1 to high fiber vs isocaloric control diet.

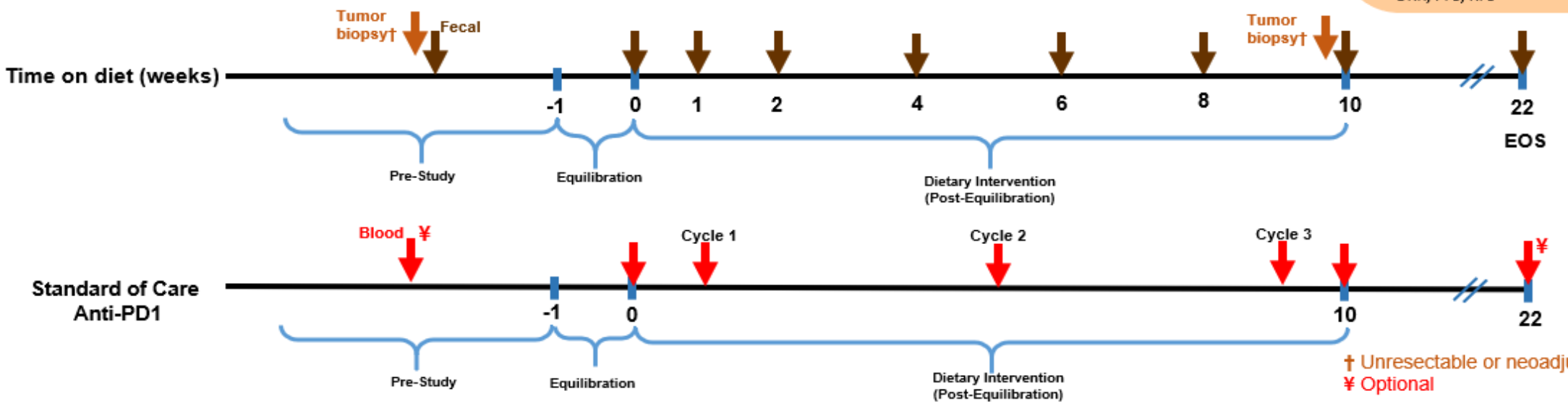
High Fiber (n=38)
50g fiber/day
↑↑↑ Diverse whole grains, fruits, and vegetables

AICR/ACS Backbone

Isocaloric Control (n=19)
**<20g fiber/day
AICR/ACS backbone

Primary Endpoint:
- Establish the effects of diet intervention on structure and function of the gut microbiome

Secondary Endpoints:
- Systemic and tumor immunity
- Gut metabolic output and systemic metabolism
- Adherence
- Quality of Life
- Safety
- Determine fiber content 70% of participants are able to tolerate
- ORR, PFS, RFS



† Unresectable or neoadjuvant arms only
¥ Optional

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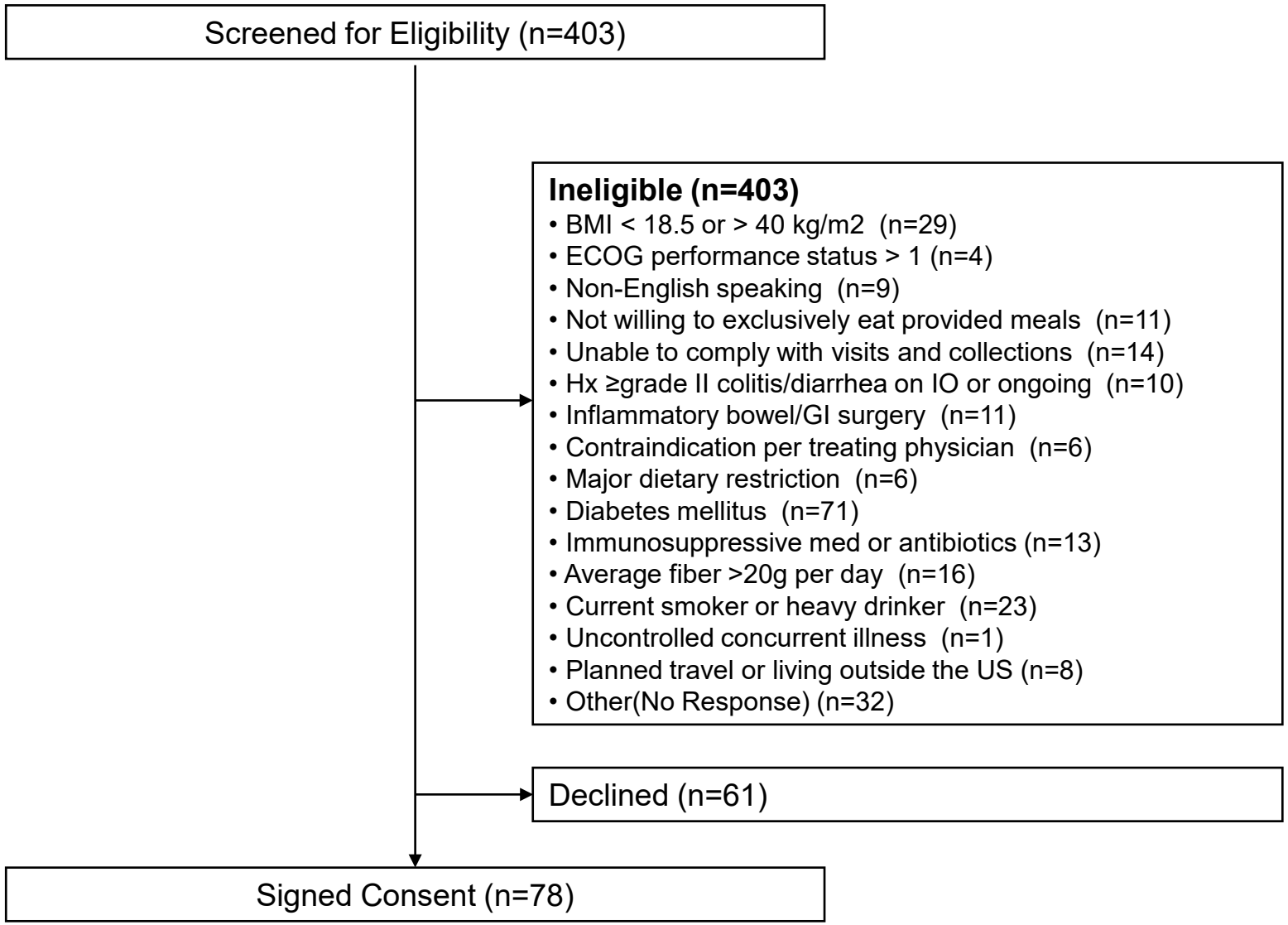
DIET 2.0



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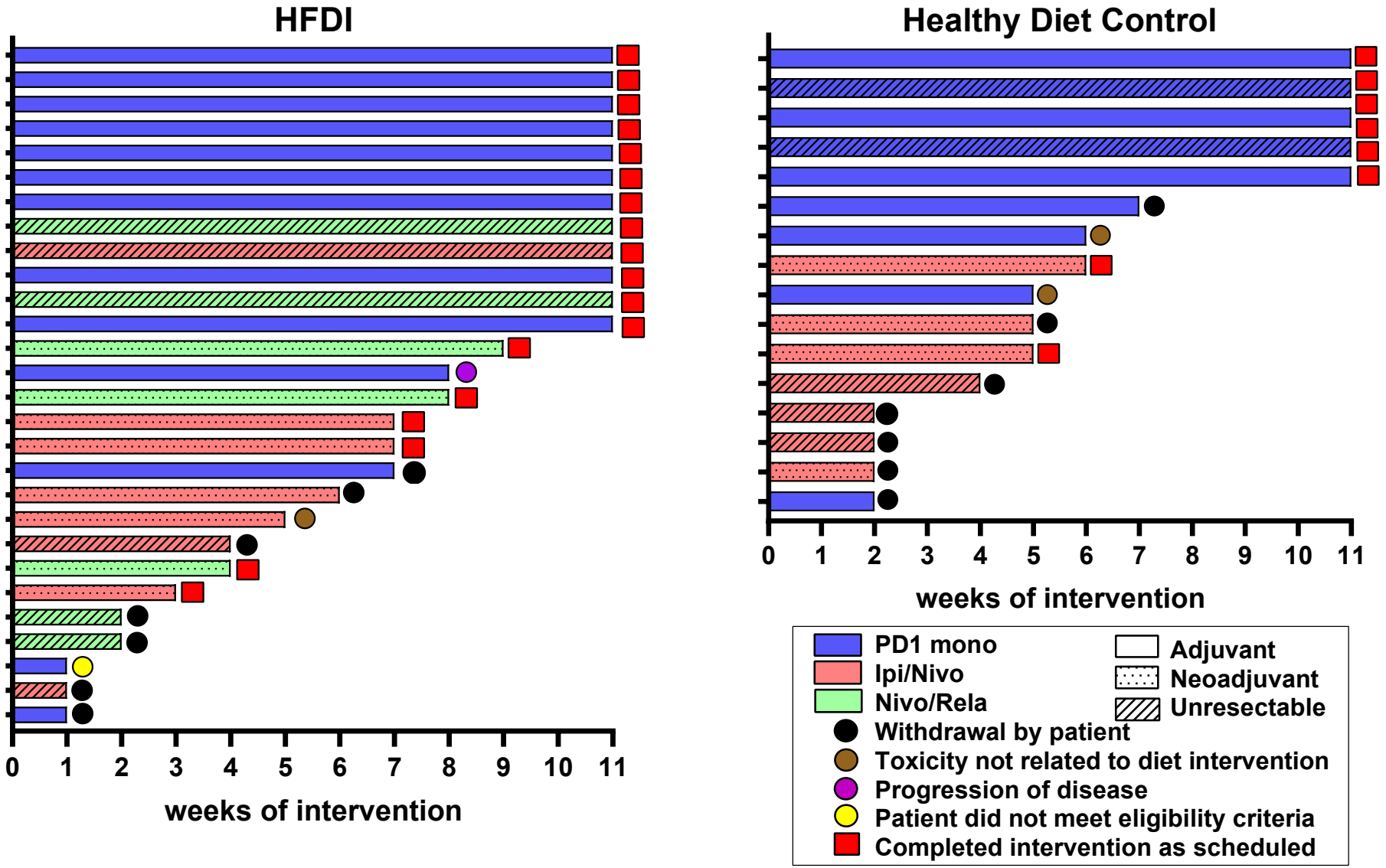
DIET 2.0: Time on study and reason for treatment discontinuation



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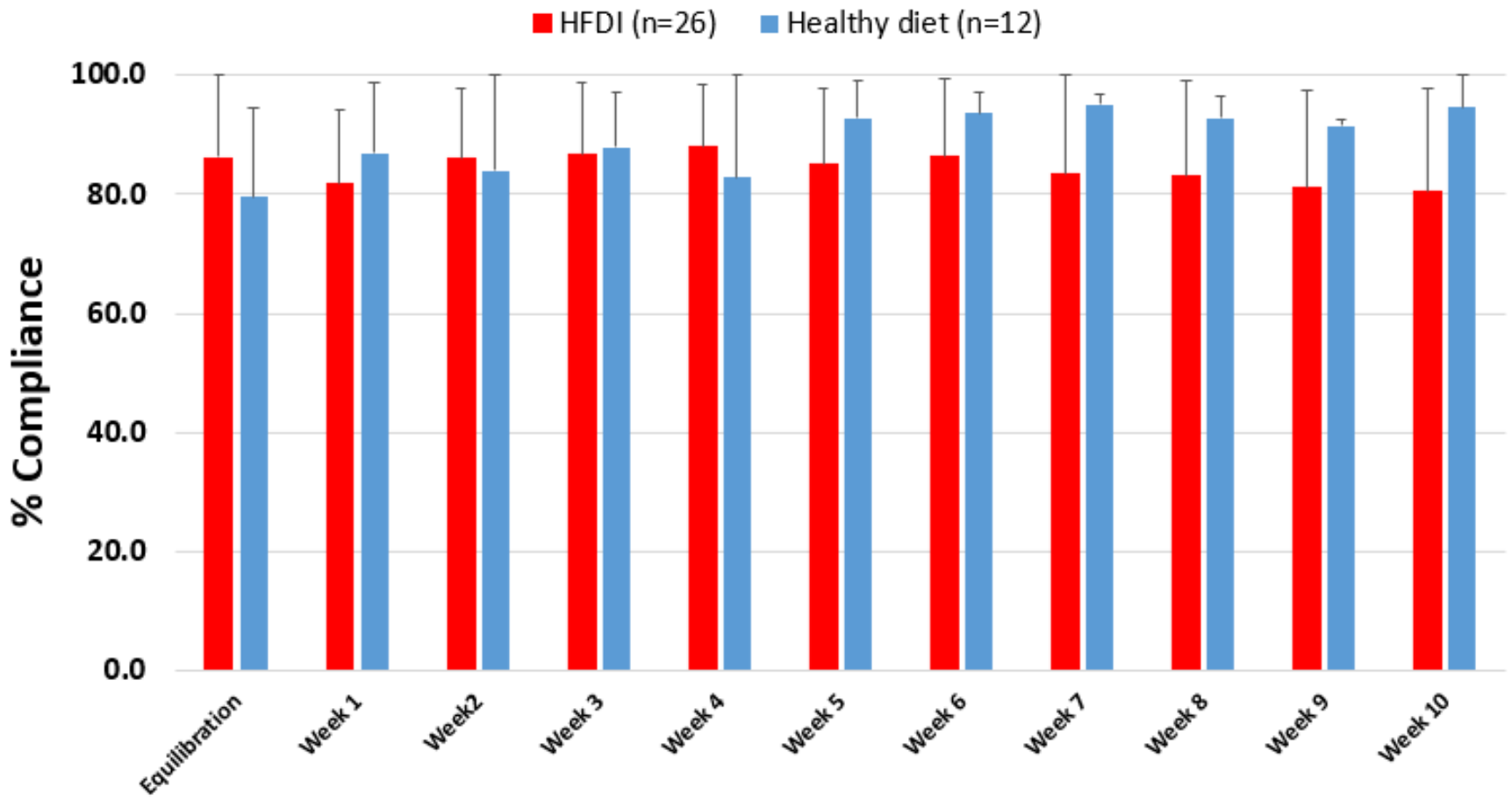
DIET 2.0 compliance
Dietary fiber ramp-up from 30g to 50g via whole foods in HFDI arm



** Data incomplete in 6 patients

Recently completed: PLEASE DO NOT SHARE OR POST

DIET 2.0: adverse events in melanoma patients

	Healthy Diet (n=15)			HFDI (n=29)		
Type of AEs	Grade 1	Grade 2	Total for all grade	Grade 1	Grade 2	Total for all grade
Any diet-related AE	5 (33%) PD1 mono 4 Ipi/Nivo 1	2 (13%) PD1 mono 1 Ipi/Nivo 1	7 (47%) PD1 mono 5 Ipi/Nivo 2	9 (31%) PD1 mono 4 Ipi/Nivo 4 Nivo/Rela 1	6 (21%) PD1 mono 4 Ipi/Nivo 2	15 (52%) PD1 mono 8 Ipi/Nivo 6 Nivo/Rela 1
Abdominal pain	2 (13%)	1 (7%)	3 (20%)	2 (7%)	1 (3%)	3 (20%)
Anorexia				2 (7%)		2 (7%)
Bloating	1 (7%)		1 (7%)	2 (7%)	1 (3%)	3 (10%)
Constipation	5 (33%)		5 (33%)	3 (10%)		3 (10%)
Diarrhea	2 (13%)	1 (7%)	3 (20%)	4 (14%)	3 (20%)	7 (24%)
Flatulence	2 (13%)		2 (13%)	5 (17%)	2 (7%)	7 (24%)
Hyperglycemia					1 (3%)	1 (3%)
Nausea				1 (3%)		1 (3%)
Weight Loss				4 (14%)		4 (14%)

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DIET 2.0: adverse events in melanoma patients

Type of AEs	Healthy Diet (n=15)			HFDI (n=29)		
	Grade 3	Grade 4	Total for grade III/IV	Grade 3	Grade 4	Total for grade III/IV
irAE	3 (20%) PD1 mono 2 Ipi/Nivo 1		3 (20%) PD1 mono 2 Ipi/Nivo 1	8 (28%) PD1 mono 4 Ipi/Nivo 4	1 (3%) Nivo/Rela 1	9 (31%) PD1 mono 4 Ipi/Nivo 4 Nivo/Rela 1
Autoimmune encephalitis	1 (7%)		1 (7%)			
Arthralgia				1 (3%)		1 (3%)
Bell's palsy				1 (3%)		1 (3%)
Colitis	1 (7%)		1 (7%)	2 (7%)		2 (7%)
Dyspnea				1 (3%)		1 (3%)
Fatigue				3 (10%)		3 (10%)
Immune-related hepatitis				1 (3%)		1 (3%)
Neutrophil count decreased					1 (3%)	1 (3%)
Optic neuritis	1 (7%)		1 (7%)			
Peripheral sensory neuropathy				1 (3%)		1 (3%)
Rash maculo-papular/Pruritus				1 (3%)		1 (3%)
Serum amylase increased				1 (3%)		1 (3%)
Type I diabetes	1 (7%)		1 (7%)			

Rate of Grade III/IV irAEs:
Ipi/Nivo treated= 33%
Nivo/Rela= 14%
PD1 mono = 27%

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Microbiome-targeting dietary intervention trials in melanoma ICB

Jennifer McQuade

- **Diet 2.0 NCT04645680 Effect of Diet on the Immune System in Patients With Stage III-IV Melanoma Receiving Immunotherapy, completed**

ASCO 2024

- PreFED NCT06250335 Impact of a Prebiotic Food-enriched Diet (PreFED) in Combination With Ipilimumab/Nivolumab Combination Immune Checkpoint Blockade (ICB) in ICB-refractory Melanoma Patients, recruiting
  - + Unresectable metastatic, newly funded by NCI
  - + Neoadjuvant, newly funded by American Cancer Society

- To progress to a large, multisite trial, we need an effective, scalable strategy that can be delivered as part of the usual care and management plan, similar to prescriptive dietary regimens in other clinical settings that can be personalized and adapted to manage the underlying inflammatory process and symptom burden in parallel with drug therapies

PreFED

	Snack Menu	Prebiotic Food Servings
Day 1	Sweet potato chips, roasted garlic hummus	2.9
Day 2	Black bean brownie, raspberry chia seed jam	2.7
Day 3	Banana muffin, succotash	3.1
Day 4	Granola, sauteed brussel sprouts	2.9
Day 5	Cocoa dusted almonds, jicama fries	3.1
Day 6	Dehydrated apples, crunchy chickpeas	3.0
Day 7	Berry & flax oatmeal, crunchy edamame	3.3

Diet Intervention

Pre-Diet Intervention | **Snack** | **Counseling**

	Baseline dietary fiber (g/1000 kcal)	Baseline diet quality score	Snack compli-	Avg Daily Prebiotic Servings on Own	Avg Daily Prebiotic Servings Consumed
Avg	9.3	67.1	93.9%	3.9	6.5
(min, max)	(6.4, 11.3)	(58.7, 75.7)	(91%, 100%)	(2, 5.5)	(4.4, 8)

Motivational Interviewing

Through open questions, affirmation, reflective and empathetic listening, seek to understand the patient's own motivations. Summarize strategies to empower the patient.

Incentive (Support) Strategies

Provide ready-to-eat PreFED snacks, easy to follow shopping lists and recipes with consistent and personalized follow-up.

= 1 cup

Education

Through PreFED handouts, visual aids and interactive discussions, teach concepts and adaptive strategies to increase and maintain prebiotic food intake.

Self-monitoring

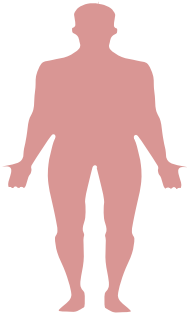
Patients observe and record prebiotic food intake to track success, identify challenges and receive feedback on progress.

10 years ago: How influential can dietary habits REALLY be to a patient with cancer? You have the tumor, the treatment, the side effects…

Today: Diet can modulate the gut microbiome, immune function, inflammatory pathways, tumor intrinsic and extrinsic factors…

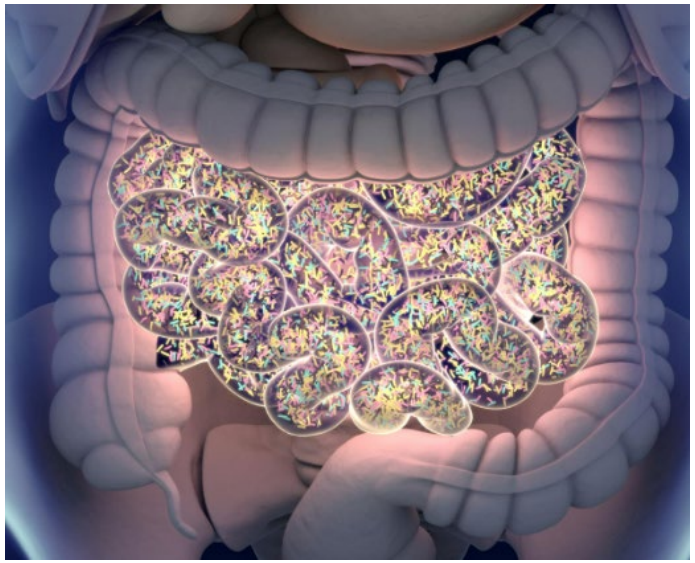
Chicken vs. egg challenge in toxicity/side effects (inpatient monitoring)

Should we **pre-screen** the microbiome (or diet) of patients



What strategy should we use to **modulate** the microbiome?

Do we need to recommend a specific diet before / after microbiome modulation to **support** or sustain the microbes?



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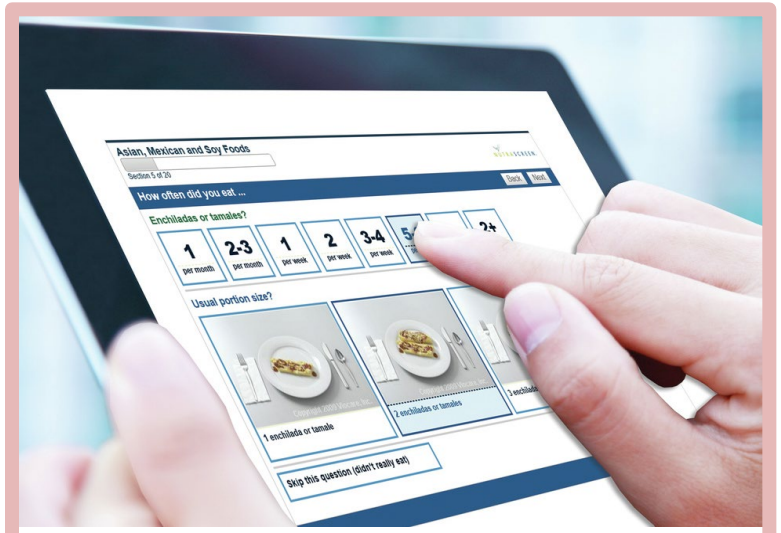
Contact Us →

MD Anderson Bionutrition Research Core

Eating habits are a form of high-dimensional data. We use validated methods and tools to capture dietary data in free-living individuals who eat unique foods and recipes that define their overall habits and nutrient intake.

Human feeding studies parallel preclinical designs. Through our metabolic research kitchen, we conduct precise dietary manipulation in short-term, but intensive human trials to measure biological effects or pharmacokinetics.



Precision nutrition = NIH priority

Thank you to our patients who give their precious time and energy to research - and to the families that support them!

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NIH NATIONAL CANCER INSTITUTE

American Cancer Society®

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Duncan Family Institute

Melanoma Research Alliance

Andrew Sabin Family Fellowship

Moon Shot

Patient Mosaic

Additional peer-reviewed foundation/philanthropic support for diet studies:

Mark Foundation for Cancer Research

Seerave

Elkins Foundation

Rising Tide